Citation:

Lajous M, Boutron-Ruault MC, Fabre A, Clavel-Chapelon F, Romieu I. Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. *Am J Clin Nutr.* 2008 May;87(5):1384-91.

PubMed ID: 18469262

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

- To evaluate carbohydrate intake, glycemic index, glycemic load, and fiber intake and the subsequent risk of overall and hormone receptor-defined breast cancer among postmenopausal women.
- For dietary carbohydrate, to examine these associations at different levels of anthropometric markers of insulin resistance

Inclusion Criteria:

- Women born between 1925 and 1950 and insured with MGEN, a French health insurance scheme primarily covering teachers
- Analysis was restricted to postmenopausal women

Exclusion Criteria:

- Miscoded questionnaires (n = 2,104)
- Respondents did not give consent to MGEN in case of dropout (n = 985)
- Unreasonable report of total energy intake
- Those who had reported cancer diagnosis before responding to the dietary questionnaire (n = 4,500)
- Those with unavailable follow-up information after the questionnaire (n = 901)

Description of Study Protocol:

Recruitment

- The E3N study was established in 1990-1991 when 98,995 women born between 1925 and 1950 and insured with MGEN, a French health insurance scheme primarily covering teachers, completed a mailed questionnaire on their lifestyle and medical history.

- 62,739 postmenopausal women from the E3N French study completed a validated dietary history questionnaire in 1993.
- The E3N cohort represents the French component of the European Prospective Investigation into Cancer and Nutrition
- Follow-up questionnaires were sent in 1992, 1993, 1994, 1997, 2000 and 2002 to ascertain newly diagnosed diseases

Design: Prospective Cohort Study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Nutrients were categorized into quartiles and energy-adjusted with the regression-residual method
- Cox model-derived relative risks were adjusted for known determinants in breast cancer
- Multivariate analyses were adjusted for age, 2-year follow-up period, region of residence, education, family history of breast cancer, history of benign breast disease, age at menarche, parity, breastfeeding, years since last use of oral contraceptives, age at menopause, years of hormone replacement therapy use, regular mammographic evaluation, height, physical activity, BMI, vitamin supplement use, and intakes of calories, folate, alcohol, carbohydrate and fiber
- To test for trend, the median value for each quartile was used as a continuous variable
- Analyses were stratified by BMI and waist circumference when information was available

Data Collection Summary:

Timing of Measurements

- Postmenopausal women completed a validated dietary history questionnaire in 1993
- Follow-up questionnaires were sent in 1992, 1993, 1994, 1997, 2000 and 2002 to ascertain newly diagnosed diseases

Dependent Variables

- Incidental cases of breast cancer were initially identified by self-report
- Physicians were individually contacted to obtain pathology reports and information on estrogen receptor and progesterone receptor status
- Deaths in the cohort were identified by reports from family members, the postal service, and the MGEN health insurance database

Independent Variables

- Carbohydrate and fiber intakes
- Glycemic index and glycemic load
- Usual dietary intake during the past year was assessed through a 208-item food frequency questionnaire
- Nutrient intakes calculated with French food composition table

Control Variables

- Age
- 2-year follow-up period
- Region of residence
- Education
- Family history of breast cancer
- History of benign breast disease
- Age at menarche
- Parity
- Breastfeeding
- Years since last use of oral contraceptives
- Age at menopause
- Years of hormone replacement therapy use
- Regular mammographic evaluation
- Height
- Physical activity
- BMI
- Vitamin supplement use
- Intakes of calories, folate, alcohol, carbohydrate and fiber

Description of Actual Data Sample:

Initial N: 77,613 dietary questionnaires collected from original cohort of 98,995 women.

Attrition (final N): After application of exclusion criteria, 62,739 postmenopausal women in final analysis

Age: mean 53 ± 7 years (range 42 - 72 years)

Ethnicity: not mentioned

Other relevant demographics:

Anthropometrics

Location: France

Summary of Results:

Relative Risks and 95% Confidence Intervals According to Quartile of Intake and Stratified by BMI

Variables	Median intake (g/day)	BMI < 25	BMI > 25	P for interaction
Carbohydrate Intake				0.58
Q1	177	1.00	1.00	
Q2	211	1.02 (0.88, 1.20)	1.27 (0.97, 1.66)	
Q3	236	1.03 (0.88, 1.21)	1.12 (0.83, 1.50)	
Q4	267	1.04 (0.89, 1.20)	1.07 (0.77, 1.49)	

P for trend		0.68	0.72	
Overall Glycemic Index				0.054
Q1	44.3	1.00	1.00	
Q2	52.4	1.07 (0.91, 1.25)	1.08 (0.80, 1.44)	
Q3	58.5	1.10 (0.94, 1.28)	1.18 (0.88, 1.59)	
Q4	65.6	1.09 (0.93, 1.28)	1.35 (1.00, 1.82)	
P for trend		0.28	0.04	
Dietary Glycemic Load				0.10
Q1	84	1.00	1.00	
Q2	111	1.05 (0.90, 1.22)	1.05 (0.79, 1.38)	
Q3	134	1.04 (0.88, 1.22)	1.37 (1.03, 1.82)	
Q4	165	1.08 (0.92, 1.28)	1.22 (0.90, 1.67)	
P for trend		0.38	0.09	

Key Findings

During a 9-year period (410,314 person-years), 1,812 cases of pathology-confirmed breast cancer were documented through follow-up questionnaires.

1,595 cases were invasive and 217 in situ.

Among overweight women, we observed an association between glycemic index and breast cancer ($RR_{Q1\text{-}Q4}$: 1.35, 95% confidence interval: 1.00, 1.82, P for trend = 0.04).

The association was absent for women with BMI < 25.

For women in the highest category of waist circumference, the $RR_{Q1\text{-}Q4}$ was 1.28 (95% confidence interval: 0.98, 1.67, P for trend = 0.10) for carbohydrates, 1.35 (95% confidence interval: 1.04, 1.75, P for trend = 0.01) for glycemic index, and 1.37 (95% confidence interval: 1.05, 1.77, P for trend = 0.003) for glycemic load.

There was also a direct association between carbohydrate intake, glycemic load, and estrogen receptor-negative breast cancer risk.

Dietary carbohydrate and fiber intakes and glycemic index and glycemic load were not associated with overall breast cancer risk.

Author Conclusion:

In conclusion, in this population of postmenopausal women we observed an association between rapidly absorbed carbohydrates and breast cancer risk among overweight women and women with large waist circumference. We also observed an increase in the risk of estrogen receptor-negative breast cancer with increasing carbohydrate and dietary glycemic load intakes. These associations should be further explored in studies with a more precise characterization of metabolic and hormonal receptor status.

Reviewer Comments:

Authors note the following limitations:

- *Single dietary assessment*
- *Lack of information about waist circumference in a subset of women*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes

3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A

6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	No
7.1.	Were primary and secondary endpoints described and relevant to the question?	No
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	No
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	N/A
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes

	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes